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CORRESPONDENCE

Letters to the Editor

Instantaneous Wave-Free Ratio

Numerically Different, But Diagnostically Superior to FFR? Is Lower Always Better?

We congratulate Johnson et al. (1) on their paper. That this field evolves rapidly is an understatement: As presented in RESOLVE (2) and discussed in the editorial by Samady and Gogas (3), the data of Johnson et al. (1), analyzed by an independent core lab using the standard instantaneous wave-free ratio (iFR) algorithm, arrived at very different conclusions.

We note the authorship group includes the innovators of the hyperemic stenosis resistance (HSR) index, which genuinely assesses epicardial resistance using pressure and flow. HSR has been consistently found to be a better predictor of ischemia than fractional flow reserve (FFR) (4). It therefore provides a unique opportunity to act as arbiter when FFR and iFR disagree. In the CLARIFY study (5), we found that when HSR was used as the reference standard, the ability of iFR to predict ischemia was equivalent to that of FFR.

Similarly, as previously reported by Nils P. Johnson, MD, MS (personal communication, December 19, 2012), is the HSR adjudication in the Johnson et al. analysis (Table 1) correct? We ask because it is not demonstrated clearly in the paper. Do the authors consider this lower-than-expected agreement in FFR to be due to one of the many known pitfalls of FFR measurements or perhaps due to the failure to achieve maximal hyperemia? Added clarity on this matter would permit a more complete comparison of the 2 indexes and perhaps lead to somewhat different conclusions.

Clear answers to these questions could elevate this already foundational paper into a landmark, overturning the decades-long dogma of the necessity of maximal hyperemia.

Table 1 Diagnostic Accuracy of iFR and FFR to Detect Ischemia as Identified by Hyperemic Stenosis Resistance

	FFR	iFR
Sensitivity, %	95.0	95.0
Specificity, %	80.0	88.0
Diagnostic accuracy, %	82.5	89.2

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio.

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Please note: Dr. Davies holds patents pertaining to this technology, which is under license to Volcano Corporation. Drs. Sen, Petraco, and Nijjer have received research consumable support from Volcano. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Reply

Dr. Sen and colleagues fail to see their own contradiction by colorfully calling for "overturning the decades-long dogma of…hyperemia" yet simultaneously proposing the *hyperemic* stenosis resistance (HSR) as a reference standard (1). Only cognitive dissonance could allow "dogma" to serve as a reasonable arbiter.

Although HSR has been proposed as a physiological index of stenosis severity, currently its limited supporting data come from a handful of publications at a single institution over the past 10 years. By contrast, fractional flow reserve (FFR) has a robust, extensive, multicenter evidence base including now 3 randomized, controlled trials of clinical outcomes.

The statement by Dr. Sen and colleagues is simply incorrect that "RESOLVE…arrived at very different conclusions" from those in our paper. Using the proprietary Volcano algorithm for instantaneous wave-free ratio (iFR), the RESOLVE registry (2) reproduced exactly the extremely linear relationship ($r^2 = 0.95$; $p < 0.001$) between rest Pd/Pa and iFR, as in our paper's Figure 5, and the "intertwining" of adenosine versus FFR agreement curves, as in our

paper's Figure 3B. Rest Pd/Pa offers the same diagnostic performance as iFR compared with FFR.

Furthermore, the reproducibility claim by Dr. Sen and colleagues regarding "lower-than-expected agreement in FFR" contradicts the published literature. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice) demonstrated 95% limits of agreement for repeated FFR measurements of ±0.04, narrower than the wider ±0.07 variability in iFR (3).

We emphasize that *their* table does *not* appear in any of *our* publications, abstracts, or conference presentations. At best, the table constitutes misattribution. Worryingly, such misattribution in their letter parallels that at their public, not peer-reviewed, website (4) and conference presentations. Specifically, the quoted words "are most accurately assessed" attributed to Gould do not appear in this decades-old and apparently dogmatic paper (5), either exactly or in spirit. We demand that Sen and colleagues constrain their speculation to the literature as published.

Resting electrocardiography, echocardiography, and perfusion imaging play key roles in daily cardiology practice. However, the stress versions of these tests often prove more useful for triage to invasive cardiac catheterization. Do Sen and colleagues only offer "rest tests" to their patients instead of stress tests?

To answer the question posed in the title of their letter, we agree that lower is *not* better–for diagnostic accuracy or patient survival.

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B-Type Natriuretic Peptide Levels in Heart Failure Patients With Preserved and Reduced Ejection Fraction

van Veldhuisen et al. (1) reported that B-type natriuretic peptide (BNP) levels are lower in patients with heart failure with preserved ejection fraction (HFPEF) than in patients with HF with reduced left ventricular (LV) EF (≤40%) and that for a certain level of BNP the prognosis in patients with HFPEF is as poor as in those with reduced LVEF.

According to the European Society of Cardiology guidelines the diagnosis of HFPEF requires 4 conditions: symptoms of HF, typical signs of HF, normal or only mildly reduced LVEF with left ventricle with normal dimensions, and relevant structural heart disease (LV hypertrophy/left atrial enlargement) and/or diastolic dysfunction. Importantly, the structural or functional abnormalities are mostly assessed by echocardiography. Echocardiographic measures such as increased left atrial volume index (volume >34 ml/m^2), LV filling pressure, or abnormalities of the mitral inflow pattern and tissue velocities are substantial evidence of the presence of HFPEF (2).

In the current study systematic echocardiographic evaluations to examine diastolic dysfunction were not performed. Nevertheless, the authors still report that echocardiography was done in more than 85% of their study population. Unfortunately, no echocardiographic parameters are shown. It would be valuable to also provide information on the echocardiographic values that could give further insight into the determinants of a high or low level of BNP in patients with HFPEF.

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Reply

We thank Dr. Haeck for his comments on our study regarding the use of echocardiography (1). The diagnosis of heart failure with preserved ejection fraction (HFPEF) is difficult, and requires 4